THERAPEUTIC ADVANCES in
Medical Oncology

Brief Report

Adjuvant and neoadjuvant chemotherapy for MSI early gastric cancer: a systematic review and meta-analysis

Ther Adv Med Oncol

2024, Vol. 16: 1–9

DOI: 10.1177/17588359241231259

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Abstract

Background: Perioperative chemotherapy (CT) is an established therapeutic approach for patients diagnosed with stage IB–III gastric cancer (GC).

Objectives: This study aimed to investigate the efficacy of this approach in individuals with GC exhibiting high microsatellite instability (MSI-H).

Design: A systematic review was conducted, including studies that provided data on (neo) adjuvant CT outcomes in patients with MSI-H GC.

Methods: Systematic searches were conducted in PubMed, Cochrane Central of Controlled Trials, and Embase databases. Data were aggregated using hazard ratios (HRs) to compare overall survival between CT and surgery.

Results: Data analysis from 23 studies, including 22,011 patients, revealed that the prevalence of MSI-H is 9.8%. Administration of adjuvant or perioperative CT did not significantly reduce the risk of death or relapse in patients with MSI-H GC (HR = 0.8, 95% CI 0.54–1.16; $p = 0.24$ and HR = 0.84, 95% CI 0.59–1.18; $p = 0.31$, respectively).

Conclusion: Chemotherapy did not benefit patients diagnosed with MSI-H nonmetastatic GC but rather will be integrated with immune checkpoint inhibitors in the near future.

Keywords: adjuvant, chemotherapy, gastric cancer, meta-analysis, MSI, neoadjuvant, survival

Received: 16 October 2023; revised manuscript accepted: 22 January 2024.

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Introduction

Globally, gastric cancer (GC) ranks as the fifth most common malignancy, with an incidence of 1,089,103 new cases per year, and it is the fourth leading cause of cancer-related death, with 768,793 fatalities in 2020. The incidence of GC varies geographically, being more frequent in Asia, Eastern and Central Europe, and South America.[1] Radical gastrectomy remains the definitive treatment for gastric cancer. However, a multimodal treatment approach is necessary to improve outcomes in the early and advanced stages, particularly with lymph node involvement or in stages greater than T1 (stages IB–III).

A multidisciplinary team, including oncologists, gastroenterologists, radiologists, pathologists, and surgeons, collaboratively reviews and discusses each case to formulate a tailored preoperative management plan. This plan is usually based on individual factors such as tumor and molecular characteristics, clinical and surgical staging, overall health, and personal preferences, aiming to maximize the chances of successful surgical resection and improve long-term outcomes. According to NCCN and ESMO guidelines, perioperative treatment with a triplet regimen is the preferred option for fit patients.[2,3] Adjuvant (radio)chemotherapy is another viable option for patients undergoing less than D2 lymph node dissection.[4–6]

In all newly diagnosed cases of GC, a mandatory molecular characterization assessment typically

includes evaluating the microsatellite instability (MSI)/Mismatch repair (MMR) status. Four GC subtypes are recognized, each with different prognoses, clinical characteristics, and potential targeted therapies.[7]

In current clinical practice, MMR deficiency (dMMR) is evaluated by performing immunohistochemistry (IHC) to assess the nuclear expression of DNA mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2). MSI status is determined at the gene expression level of microsatellite markers using polymerase chain reaction (PCR) or next-generation sequencing (NGS) tests.[8] MSI-H or dMMR status, associated with a better prognosis, is present in about 8–10% of GC cases. In metastatic GC, therapy with immune checkpoint inhibitors plays a significant role and represents the standard of care in advanced settings where PD-L1 is expressed. The most significant benefit is observed in patients with MSI-H tumors. Ongoing trials are investigating the use of immunotherapy in neoadjuvant and perioperative settings for MSI-H GC.[9–14]

This meta-analysis was designed to determine whether neoadjuvant chemotherapy offers an advantage to patients with MSI-H GC.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.

Eligibility criteria and search strategy

We included prospective and retrospective studies that assessed the efficacy of adjuvant, perioperative, and neoadjuvant CT in patients with nonmetastatic MSI-H GC. All patients with early-stage or locally advanced disease were included in this meta-analysis, regardless of the histological subtype, sex, race, and country. We excluded patients who received immune checkpoint inhibitors in the adjuvant or neoadjuvant setting.

We searched several electronic databases on 30 April 2023, including Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, and EMBASE, using the following terms: (*gastroesophageal* or *gastric or stomach) and (cancer or carcinoma), and chemotherapy and (dMMR or MSI or microsatellite or mismatch repair)*. We also manually checked eligible studies' reference lists and cited articles.

Data extraction and statistical analysis

Two authors (FP and MA) independently screened the titles and abstracts of the articles identified in the search and assessed study eligibility based on the full texts. Disagreements between the two authors were resolved by discussion. We performed abstract and full-text screening using the prescribed criteria. Using a standardized data collection form, two authors (FP and MA) independently extracted the data from the included studies. All disagreements were resolved by discussion. Two authors (FP and MA) independently evaluated the risk of bias using the ROBINS tool.[15] A third author (GT) discussed any disagreements between the two authors. We used the Newcastle–Ottawa scale to assess the methodological quality of the observational studies.[16]

We performed a meta-analysis using the Review Manager software (RevMan 5.4.1; Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark). The primary endpoint was overall survival (OS), and the secondary endpoint was disease-free survival (DFS). We pooled the data using a random-effects model. We calculated the pooled hazard ratios (HR) with 95% confidence intervals (CIs) for the two primary endpoints. Statistical heterogeneity was evaluated by visual inspection of the forest plots and I^2 statistics.

We performed a subgroup analysis according to trial quality (Nottingham-Ottawa Scale (NOS) >7), median follow-up (at least 5 years), country, and type of CT (adjuvant *versus* perioperative/neoadjuvant). A two-tailed p-value of less than 0.05 was considered statistically significant.

Results

Figure 1 illustrates a flow diagram of the study selection process. After screening the titles and abstracts of the identified articles, 76 relevant ones were identified. Eligibility assessment based on the full text resulted in the final inclusion of 23 records.[17–39]

The characteristics of the 23 included studies are summarized in Table 1. Two retrospective studies evaluated randomized clinical trials (RCT;

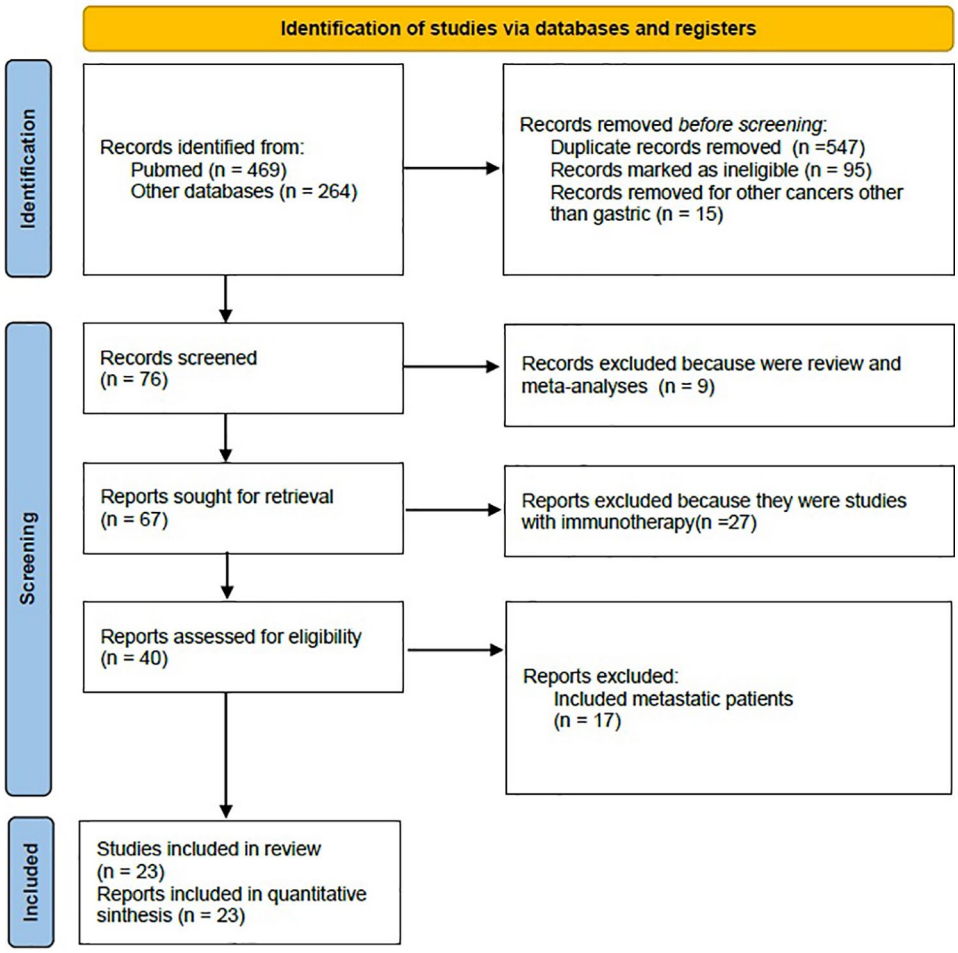

Figure 1. Flow diagram of included studies.

one meta-analysis of four RCTs and one retrospective analysis of one RCT), one case–control study, one prospective observational study, and $n=19$ retrospective series for a total of 22,011 GC patients ($n=2161$ were MSI; 9.8%).

Overall, 15 studies had a low risk of bias (65%) and 17 were of sufficient or high quality according to the NOS score (74%).

Chemotherapy was delivered in $n=3$, $n=13$, and $n=6$ studies in neoadjuvant, adjuvant, and perioperative settings, respectively.

Overall survival

Seventeen trials reported OS data. Overall, adjuvant or perioperative CT resulted in a non-significant reduction in the risk of death (HR = 0.8, 95% CI 0.54–1.16; $p=0.24$; Figure 2) with high heterogeneity ($I^2=91\%$, $p<0.01$).

Disease-free survival

Sixteen trials reported an analysis of DFS. Chemotherapy resulted in a nonsignificant reduction in the risk of relapse (HR = 0.84, 95% CI 0.59–1.18; $p=0.31$; Figure 3), with high heterogeneity ($I^2=73\%$, $p<0.01$).

Subgroup analysis

In studies with higher-quality scores (NOS score $\geqslant 7$), the risk of death with CT was similar to that in the main analysis (HR = 0.80, 95% CI 0.53–1.21; $p=0.29$). Only two papers reported median follow-up over 5 years; therefore, subgroup analysis was not performed. In both Asian populations and Western countries, the effect of CT was similar (HR = 0.71, 95% CI 0.28–1.78; $p=0.47$ and HR = 0.77, 95% CI 0.57–1.04). The effect of adjuvant CT (HR = 0.71, 95% CI 0.33–1.53; $p=0.38$) was similar to that of perioperative CT (HR = 0.72, 95% CI 0.51–1.01; $p=0.06$).

Table 1. Characteristics of included studies.

Author/years	Type of study	Median follow-up (months)	Country	No. pts (MSI + MSS)	No. MSI (CT + S *versus* S)	Type of MSI evaluation	Type of CT	Stage	OS available	DFS available	Quality	Bias
Akimoto/2023	Case–control study	NR	Japan	679	71 (41 *versus* 30)	IHC	Adjuvant	II/III	√	√	6	Low
An/2012	Retrospective	30.2	Korea	1990	170	PCR	Adjuvant	I/II/III/IV	–	√	6	Low
Kim/2020	Retrospective	71.1 in cohort 1 87.9 in cohort 2	Japan	521	203	PCR	Adjuvant	Ib/II/III	√	√	8	Low
Bermudez/2021	Retrospective	NR	Spain	142	23 (5 *versus*18)	IHC	Adjuvant	I/II/III/IV	√	–	5	High
Biesma /2022	Retrospective analysis of 1 RCT	NR	Netherland	898	74	PCR and IHC	Perioperative	I/II/III/IV	√	√	6	Moderate
Cai/2020	Retrospective	NR	China	690	57 (42 *versus*15)	IHC and PCR	Neoadjuvant	III	√	√	6	Uncertain
Kim /2015	Retrospective	47	Korea	1276	105 (58 *versus*47)	PCR	Adjuvant	II/III	√	–	6	Low
Hashimoto/2019	Retrospective	58.4	Japan	285	28 (12 *versus* 16)	IHC e PCR	Neoadjuvant	III/IV	–	√	7	Low
Guan /2021	Retrospective	NR	China	890	196	IHC e PCR	Adjuvant-1 line	I/II/III/IV	√	√	5	Low
Dai /2019	Retrospective	NR	China + western	429	102 (32 *versus* 70)	PCR	Adjuvant	IB/II/III	√	√	5	Uncertain
Kohlruss /2021	Retrospective	60.7	Germany	717	67 (32 *versus* 35)	PCR	Neoadjuvant	II/III	√	–	7	Low
Oh/2021	Retrospective	70	Korea	838	100 (40 *versus* 60)	PCR	Adjuvant CT e CTRT	IIA	–	√	8	Low
Pietrantonio/2019	Individual-patient-data meta-analysis of four RCTs*	NR	Asian and European	1556	121 (88 *versus* 33)	PCR and IHC	Perioop and adjuvant ± RT	II/III	√	√	8	Low
Ramos/2019	Retrospective	36,9	Brazil	171	31	IHC	Adjuvant CT/CTRT	II/III	√	√	6	Moderate
Quaas/2022	Retrospective	NR	Netherland	1307	115 (39 *versus* 76)	PCR and IHC	Perioperative CT/CTRT	I/IV	√	–	6	Low
Neto do Nascimento/2023	Retrospective	41	Portugal	137	37 (11 *versus* 26)	PCR	Perioperative CT	II/III	√	–	7	Low
Shon/2017	Retrospective	NR	Korea	699	NR	PCR/NGS	Adjuvant	II/III	√	√	5	Moderate
Stolze/2023	Retrospective	NR	Germany	223	23 (10 *versus* 13)	IHC	Perioperative CT	II/III	√	–	5	Uncertain
Vos/2022	Retrospective	34	US	535	82 (50 *versus* 32)	NGS and IHC	Perioperative, or adjuvant CT	III/IV	√	√	6	Low
Zhao-Li/2023	Prospective, observational	36	China	479	69 (54 *versus* 15)	IHC	Adjuvant	II/III	√	√	6	Low
Wang/2020	Retrospective	NR	China	444	111	IHC	Adjuvant	II/III	√	–	5	Moderate
Zhao-Fu/2023	Retrospective	NR	China	6176	293 (191 *versus* 102)	IHC	Perioperative and adjuvant	I/II/III	√	√	6	Low
Tsai/2020	Retrospective	NR	Taiwan	929	83 (59 *versus* 24)	IHC	Adjuvant	II/III/IV	√	√	6	Low

*Only analysis of MAGIC and CLASSIC trials were used.
Adj, adjuvant; CT, chemotherapy; DFS, disease-free survival; IHC, immunohistochemistry; MSI, microsatellite instability; MSS, microsatellite stable; NGS, next-generation sequencing; NR, not reported; OS, overall survival; PCR, polymerase chain reaction; RCT, randomized controlled trials; RT, radiotherapy; US, United States.

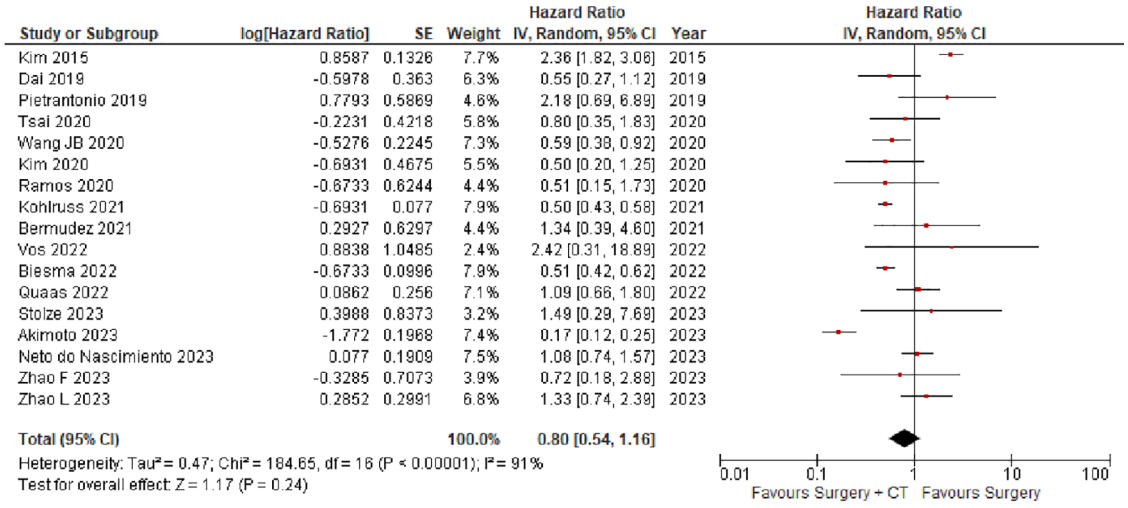

Figure 2. Overall survival with adjuvant chemotherapy *versus* surgery alone in MSI gastric cancer.
MSI, microsatellite instability.

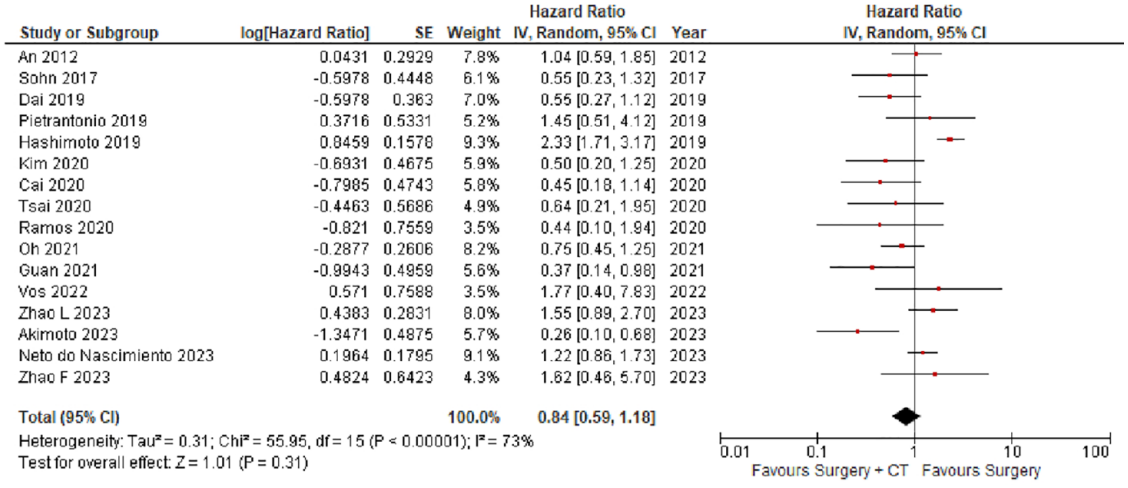

Figure 3. Disease-free survival with adjuvant chemotherapy *versus* surgery alone in MSI gastric cancer.
MSI, microsatellite instability.

Discussion

This meta-analysis was specifically designed to evaluate the effectiveness of neoadjuvant chemotherapy in a distinct subgroup of GC patients characterized by microsatellite instability-high (MSI-H) status. The primary objective was to shed light on the ambiguous benefits of both neoadjuvant and adjuvant chemotherapy in this specific patient population. Our comprehensive analysis revealed a notable absence of significant improvement in key survival metrics, namely OS and DFS, across both adjuvant and perioperative treatment settings.

A critical aspect of this study was the examination of findings from previous studies, notably those conducted by Pietrantonio *et al.* and Nie *et al.*[40,41] These inconsistencies are crucial as they underline the complex and multifaceted nature of MSI-H GC and the difference in included studies. Nie and colleagues conducted a review of only seven retrospective studies, each inherently subject to bias. By contrast, the meta-analysis by Pietrantonio *et al.*, despite the limited number of MSI-H GC cases, presents for the first time the results of an individual patient data meta-analysis. This analysis focuses on the impact of MSI status on

long-term oncologic outcomes for patients with resectable GC who were treated in large RCT.

The reduced treatment efficacy observed in these studies suggests that MSI-H GC should not be treated as a uniform disease entity. Instead, it appears to be a heterogeneous condition that demands a more nuanced and detailed molecular classification system. Such a system would enable the development of more precisely targeted treatment strategies, tailored to the unique characteristics of each patient's disease.

One of the most promising directions emerging from this meta-analysis is the observed positive correlation between MSI-H status and the efficacy of immunotherapy, particularly in patients exhibiting high PD-L1 scores. This correlation indicates a potential paradigm shift away from traditional chemotherapy toward immunotherapy, especially for those patients who demonstrate poor responsiveness to conventional chemotherapy treatments. This shift underscores the growing importance of developing personalized treatment plans based on each tumor's detailed molecular and genetic profiling. Supporting this notion, a recent meta-analysis focusing on locally advanced GC highlighted the effectiveness of therapy based on immune checkpoint inhibitors in a neoadjuvant context. According to the findings reported by Li *et al.*, the most significant benefits of this approach were seen in MSI-H patients with high PD-L1 scores.[42] An intriguing finding from the prospective phase II DANTE trial, conducted in the preoperative setting, was that the combination of 5-Fluorouracil, oxaliplatin, taxotere (FLOT) chemotherapy and atezolizumab resulted in more effective downsizing than the FLOT alone regimen [complete pathological response (pT0), 23% *versus* 15%; node-negative status (pN0), 68% *versus* 54%]. Increases in pathological regression rates were observed, particularly in cases with higher PD-L1 expression. However, the trial did not gather data on OS or DFS, which limits the ability to understand the long-term impacts of this treatment approach fully.[43] Similarly, the KEYNOTE-585 study randomized GC patients to receive either neoadjuvant and adjuvant pembrolizumab or placebo combined with chemotherapy. Differences in pathological complete responses, in favor of the experimental arm, were 37% in patients with MSI-H tumors who received pembrolizumab but only 7% in those with microsatellite stable (MSS) tumors. This was even though OS and event-free survival were similar between the pembrolizumab and placebo groups.[44]

Based on this rationale and considering the data from the metastatic setting, perioperative or neoadjuvant treatment using PD-1 inhibitors combined with chemotherapy appears to be theoretically superior to chemotherapy alone for patients with dMMR/MSI-H GC before radical surgery. For this reason, chemotherapy should probably not be abandoned but instead augmented with immune checkpoint inhibitors.

However, our meta-analysis is not without limitations. It was primarily based on retrospective studies that met specific inclusion criteria. As a result, the predictive role of MSI status in patients could not be verified through prospective, RCT. In addition, the analysis encompassed a diverse array of patient populations, disease settings (including both adjuvant and neoadjuvant contexts), surgical approaches (ranging from D1 to D2 lymphadenectomy), chemotherapy regimens (primarily older agents), and racial backgrounds. Another point of consideration is the variation in MSI assessment techniques used across the studies, which were predominantly conducted at the time of surgery rather than at diagnosis. Despite these limitations, our study stands as the most extensive and up-to-date meta-analysis evaluating the predictive role of MSI in GC treated with perioperative/adjuvant chemotherapy or surgery for localized or locally advanced disease.

The reliance on retrospective studies underscores an urgent need for more prospective, randomized trials in this area. Such studies would provide stronger, more conclusive data and would help in more clearly defining the role of MSI status in guiding treatment decisions. The diversity in patient populations, disease settings, and treatment regimens examined in our meta-analysis accurately reflects the real-world complexity of treating GC. Future research efforts should aim to embrace this diversity to ensure the findings are broadly applicable and relevant. Furthermore, the differences in MSI assessment techniques across studies present a significant challenge. Establishing a standardized, universally accepted method for MSI assessment is essential for future research, as it would ensure consistency and comparability of results across different studies.[45]

Conclusion

In conclusion, the lack of significant benefit from adjuvant or perioperative chemotherapy in patients with MSI-H GC necessitates critically reevaluating current treatment strategies for this subgroup.

There is a compelling need to integrate modern chemotherapy regimens and immune checkpoint inhibitors in both neoadjuvant and perioperative settings. Moreover, the inclusion of MSI-H GC patients in clinical and translational studies is imperative for developing more effective, personalized treatment approaches that cater to this patient subgroup's specific needs and characteristics.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Fausto Petrelli: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Software.

Maria Antista: Writing – original draft; Writing – review & editing.

Francesca Marra: Validation.

Fulvia Milena Cribiu': Validation.

Valentina Rampulla: Validation.

Filippo Pietrantonio: Validation.

Lorenzo Dottorini: Validation.

Michele Ghidini: Validation.

Andrea Luciani: Validation.

Alberto Zaniboni: Validation.

Gianluca Tomasello: Validation.

Acknowledgements
None.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Italian Ministry of Health (Ricerca Corrente 2024).

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
At the request to the corresponding author.

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Supplemental material
Supplemental material for this article is available online.

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